PET Imaging of Peripheral Nerve Tumors

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KEYWORDS

• PET • Malignant peripheral nerve sheath tumor (MPSNT) • PET/CT imaging • PET/MR imaging

KEY POINTS

- Malignant peripheral nerve sheath tumors (MPNST) are the sixth most frequent soft tissue sarcoma (STS), consisting of 5% to 10% of cases.
- Traditionally, MR imaging has been the main imaging modality to evaluate the extent and involvement of MPNT.
- The potential value of PET and PET/CT in regards to diagnosis, biopsy guidance, staging, and therapy response of MPNT are presented in the literature.
- Multimodality imaging with multiparametric hybrid PET/MR has also shown some utility in the management of peripheral nerve tumors (PNTs).
- Quantitative FDG-PET imaging used in combination with CT or MR imaging has shown great potential to discriminate benign from malignant PNTs.

INTRODUCTION

Peripheral nerve tumors (PNT) are a heterogeneous category of neoplasms that are very rare in the population. The classification of theses tumors is variable, as most of these tumors have more than one name. Furthermore, peripheral nerve sheath tumors encompass a variety of cell types, some of which are not yet completely characterized. Common classification systems are based on the presence or absence of neoplasia, whether the neoplasm is benign or malignant, and the cellular origin of the primary neoplasia.[1,2]

Malignant peripheral nerve sheath tumors (MPNST) are the sixth most frequent soft tissue sarcoma (STS), consisting of 5% to 10% of cases.[3–5] Approximately 50% of all MPNST develop sporadically, whereas the other 50% are associated with neurofibromatosis type 1 (NF1).[6–8] Patients with NF1 have an 8% to 13% lifetime risk of developing MPNST, with an incidence of 1:3500, compared with the incidence of 1:100,000 among the general population.[6] Approximately 30% of NF1-associated MPNST arise from a deeply located neurofibroma, with most of the tumors developing in the proximal upper and lower limbs.[9] Patients can present with a variety of symptoms, which may include pain, paresthesia, and neurologic deficits.[10] MPNST have a poor prognosis, with overall 5-year survival rates ranging from 20% to 50% for high-grade MPNST and a mortality of up to 75%.[11]

Diagnostic imaging of PNT is crucial for proper characterization and management. Traditionally, MR imaging has been the main imaging modality to evaluate the extent and involvement of PNT. Ultrasound and computed tomography (CT) can also be of value in select patients and may be

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used for image-guided biopsies.[12] Furthermore, bone scintigraphy may be useful to evaluate for osseous involvement.[13]

Over recent years, PET has been gaining increasing traction in the assessment of musculoskeletal tumors. The use of PET to assess disease biology at an individual level is now playing a pivotal role in personalized clinical decision making and further clinical management.[14–16] However, although the use of PET/CT is being increasingly used in patients with MPNST, its definite role within the clinical routine is still not delineated, partially because of the rarity of these tumors hindering prospective investigations with large patient groups. Here, the authors discuss the role and potential value of PET and PET/CT in regards to diagnosis, biopsy guidance, staging, and therapy response of PNT.

DIAGNOSIS AND DIFFERENTIATION BETWEEN BENIGN AND MALIGNANT PERIPHERAL NERVE TUMORS WITH FLUDEOXYGLUCOSE-PET

The diagnosis of MPNST and their distinction from benign tumors remain a clinical challenge, because the symptoms of the 2 conditions demonstrate substantial overlap. At present, CT, MR imaging, and PET are the main imaging tools used to assess and diagnose MPNST. Both CT and MR imaging are useful to define the anatomic tumor size and local invasiveness of MPNST.[17] In addition, several investigations have developed diagnostic criteria to help aid in the discrimination between benign and malignant PNT using CT and MR imaging. However, these criteria have not been reliable in distinguishing between benign and malignant PNTs, especially when tumors are inhomogeneous.[18] Thus, the main shortcoming of both CT and MR imaging is the inability to efficiently confirm malignant transformation of lesions.[17]

To address this issue, several studies have assessed the ability of fludeoxyglucose (FDG)-PET with or without CT to distinguish benign from malignant primary PNT based on a tumor's metabolic activity.[17,19–22] In general, benign PNTs depict no or low FDG uptake, whereas malignant PNTs demonstrate moderate to high FDG accumulation. In these studies, standard uptake values (SUV), a quantitative amount of FDG uptake, range between 1.0 and 3.99 in benign PNTs and between 3.1 and 21.4 in malignant PNTs.[17,23–26] In a systematic review by Tovmassian and colleagues,[19] summarizing 796 tumors from 13 various reports, FDG-PET demonstrated noteworthy difference regarding the distinction of benign from malignant PNTs (mean SUVmax: 1.93 vs 7.48) with a mean accuracy across the studies of 83.5%. Receiver operating characteristic analysis was carried out in several of the studies to determine optimal SUVmax cutoff. These values yielded cutoffs of 3.1, 3.2, 3.5, 4.1, and 6.1 to attain maximum statistical parameters of ascertaining malignant lesions.[19] It revealed that FDG-PET/CT could be valuable in the diagnosis of malignant lesions with the sensitivities ranging from 91% to 100% and specificity ranging from 72% to 95%. However, there was significant overlap in ranges of SUVmax in these studies and inadequate evidence to admit a universal cutoff value for SUVmax (**Fig. 1**).[19]

Recently, Azizi and colleagues[27] evaluated the value of FDG-PET imaging in the detection of malignant transformation of symptomatic and asymptomatic plexiform neurofibromas in 41 children with NF1. This study demonstrated overlap between the SUVmax of malignant and benign lesions, yet no malignant lesion demonstrated FDG uptake less than 3.15 (**Fig. 2**). Asymptomatic malignant lesions were diagnosed with a sensitivity of 100%, a negative predictive value of 100%, and a specificity of 45.1%. This value highlights the utility of FDG-PET in detecting malignant transformation of plexiform neurofibromas, especially in asymptomatic patients. This issue may reveal MPNST at early stages, potentially increasing the possibility of oncologically curative resections.

Dual-time-point FDG-PET has demonstrated some potential in distinction between malignant and nonmalignant PNTs.[23,28] However, PNTs have mostly shown similar FDG uptake on delayed projection, and the implication of this protocol remains unknown.[26] Multimodality imaging with multiparametric hybrid PET/MR has also shown some utility in the management of PNTs.[29,30] A few studies have assessed the combined use of FDG-PET and MR imaging in this regard.[24,31,32] Broski and colleagues[31] carried out the largest study to date assessing the performance of FDG-PET and MR imaging in a cohort of histologically proven benign and malignant peripheral nerve sheath tumors involving 38 patients with 23 benign PNSTs and 20 malignant PNSTs. In this study, FDG PET was 90% to 100% sensitive and 52.2% to 82.6% specific for diagnosing MPNST, whereas expertly interpreted MR images had a 62.5% to 81.3% sensitivity and 94.1% to 100% specificity, thus underscoring the complementary role of PET/MR imaging in the management of PNTs. In addition, as state-of-the-art PET/MR imaging becomes more common, concurrent combined PET and MR imaging offers the potential of a "one-stop-shop" imaging modality for patients.

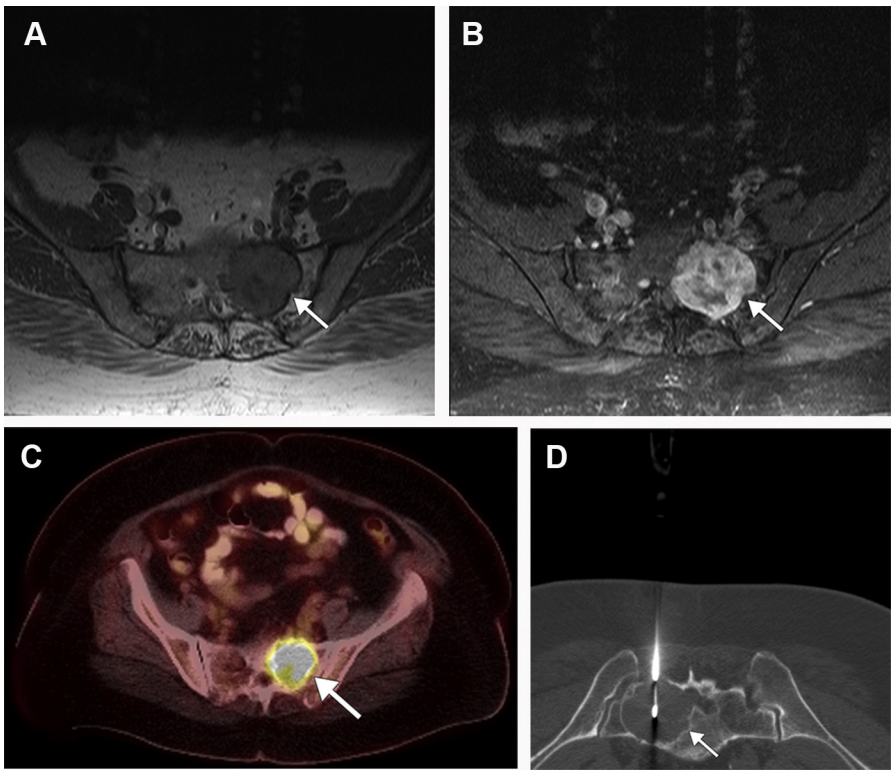

Fig. 1. A 70-year-old woman who initially presented with left paraspinal and lower extremity pain. Axial T1 (*A*) and T1 FS postcontrast (*B*) MR images demonstrate a 4.8-cm mass (*arrows*) centered in the left S1 neural foramen. 18F-FDG PET/CT (*C*) shows intense hypermetabolism with SUVmax of 8.9 (*arrow*). CT-guided biopsy (*D*) and subsequent resection (*arrow*) both came back as benign schwannoma despite the high SUVmax.

In conclusion, definitive imaging difference of benign and malignant PNTs remains a challenge. Quantitative FDG-PET imaging used in combination with CT or MR imaging has shown great potential to discriminate benign from malignant PNTs. Nevertheless, additional studies are needed, and the imaging and clinical characteristics of PNTs have not yet replaced histopathologic consideration as the gold standard for diagnosis.

GRADING OF MALIGNANT PERIPHERAL NERVE SHEATH TUMORS WITH FLUDEOXYGLUCOSE-PET

Accurate histologic grading is imperative in the assessment and management of MPNST. Preoperative imaging appraisal of the histologic grade is a challenging subject, with several contradicting results between FDG uptake (SUVmax) and histopathologic grading of MPNST.

In a study by Ferner and colleagues,[28] assessing FDG-PET/CT as a diagnostic modality for MPNST in NF1 cases with symptomatic plexiform neurofibromas, a total of 116 lesions were evaluated in 105 patients, including 80 plexiform neurofibromas, 5 atypical neurofibromas, 29 MPNST, and 2 other tumors. FDG-PET and PET/CT detected NF1-associated tumors with a sensitivity of 0.89 (95% confidence interval [CI] 0.76 to 0.96) and a specificity of 0.95 (CI 0.88–0.98); however, the SUVmax level did not predict tumor grade. Kim and colleagues[33] retrospectively investigated CT (n = 14), MR imaging (n = 16), and 18F-FDG PET/CT (n = 5) imaging characteristics of 18 different MPNST of the head and neck in 17 patients. 18F-FDG PET/CT images acquired for 5 cases depicted homogeneous (n = 3) or heterogeneous (n = 2) hypermetabolic foci with a mean SUVmax of 7.16 $\pm$ 4.57 (range, 3.2–14.6). In this study, the SUVmax correlated well with the histologic grade of the tumors: 2 with SUVmax of 3.2 and 3.9 were histologically categorized as low grade; one with SUVmax of 6.1 as intermediate grade; and 2 with SUVmax of 8.0 and 14.6 as high grade (**Fig. 3**). Warbey and colleagues[23] assessed 69 patients with NF1 with 85 lesions, including 10 atypical neurofibromas and 21 MPNST. In this study, FDG-PET was very sensitive (97%) and specific (87%) in the diagnosis of

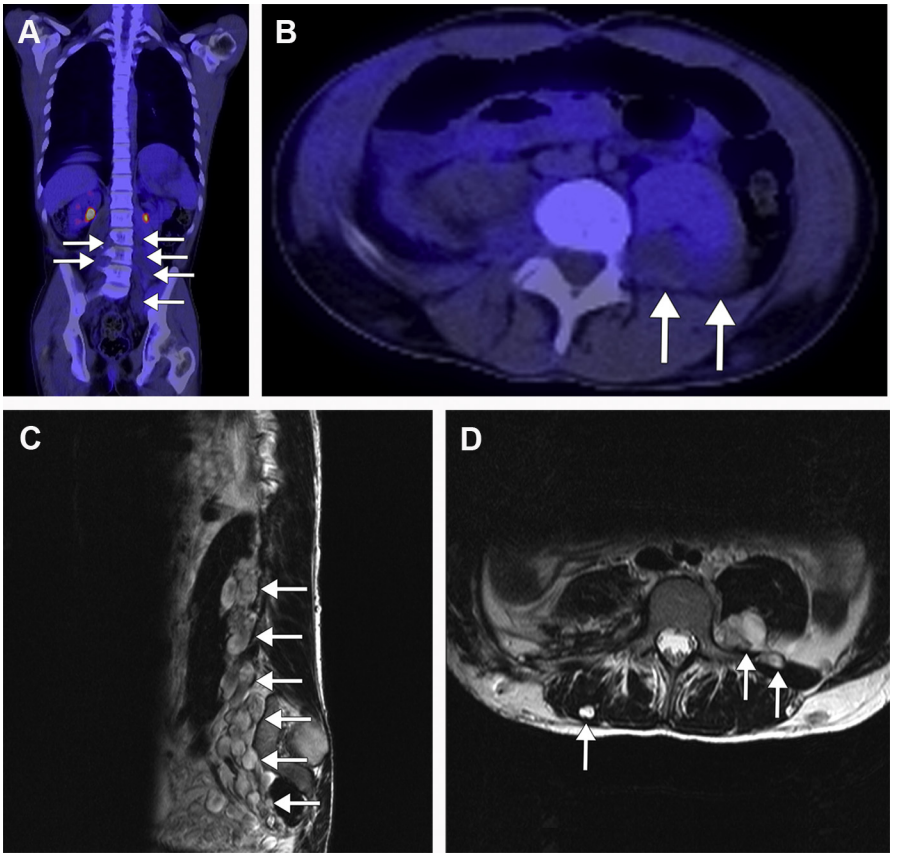

Fig. 2. A 24-year-old man with history of NF1. Coronal (*A*) and axial (*B*) 18F-FDG PET/CT and sagittal (*C*) and axial (*D*) T2-weighted MR images demonstrate numerous paraspinal masses (*arrows*). The SUVmax was 3 or less for all of these masses, indicating that these are all benign neurofibromas without need for further workup at this time.

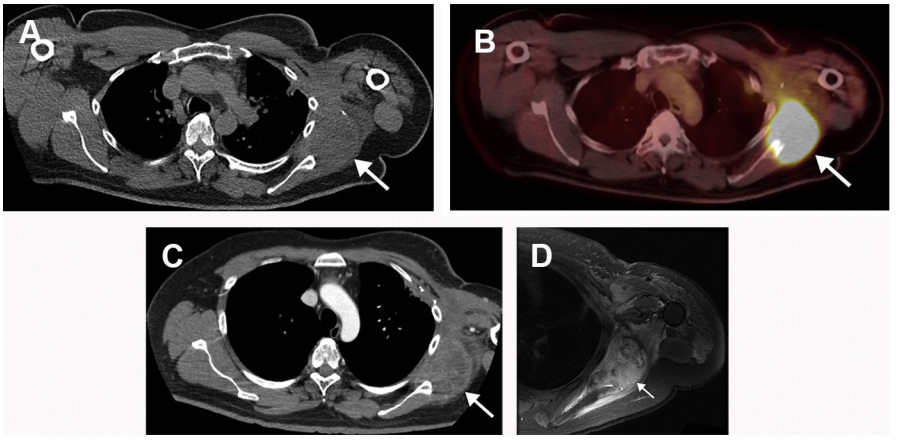

Fig. 3. A 44-year-old man with history of left axillary malignant peripheral nerve sheath tumor, status postresection with positive margins and adjuvant radiation therapy. A recent biopsy of a left chest wall mass demonstrated fibrosis on pathology. Axial noncontrast CT (*A*) demonstrates an ill-defined left chest wall periscapular mass (*arrow*). 18F-FDG PET/CT (*B*) shows intense hypermetabolism with SUVmax of 23.5 (*arrow*). Axial contrast-enhanced CT (*C*) and axial STIR MR imaging (*D*) show heterogeneous enhancement and signal intensity within this recurrent high-grade MPNST (*arrows*).

MPNST. Cardona and colleagues[34] demonstrated that MPNST have considerably higher FDG uptake in their assessment of 25 neurogenic STS.

Furthermore, schwannomas should be included in the differential diagnosis of peripheral nerve sheath tumors with low, intermediate, or high SUVs.[35] Given the considerable overlap in the SUVmax between low- and high-grade MPNST, further studies using new tracers and parameters may be helpful in discriminating high- and low-grade MPNST.[28,36]

In summary, although higher-grade tumors are typically more metabolically active than lower-grade tumors, there is currently a lack of evidence for the ability of FDG-PET to assess tumor grade in PNTs. Further studies evaluating SUV parameters and tumor grade of PNTs are needed, and biopsies with histologic analysis should be routinely performed to accurately ascertain tumor grade.

BIOPSY GUIDANCE AND STAGING OF MALIGNANT PERIPHERAL NERVE SHEATH TUMORS WITH FLUDEOXYGLUCOSE-PET/COMPUTED TOMOGRAPHY

The standard management of MPNST requires biopsy before surgical resection. One way to improve biopsy results is to leverage the metabolic data afforded by PET imaging to efficiently target and sample tissues, especially when other modalities such as radiograph, CT, or ultrasound do not clearly identify the abnormality. PET/CT-guided biopsy combines the well-established worth of anatomic information from CT with the metabolic information from FDG-PET. In a study of 26 NF1 patients with a clinical suspicion of MPNST and suspect lesion on PET/CT scan, Brahmi and colleagues[37] demonstrated a diagnostic accuracy rate of 96% with PET/CT-guided percutaneous biopsies (**Fig. 4**).

The exact role of PET-guided biopsy is not yet well established, but may be of most benefit in patients with previous inconclusive biopsy findings or findings discordant with the overall clinical and imaging data. Furthermore, large malignant lesions can be heterogeneous, and PET/CT functional imaging-driven biopsy may be of great benefit for guiding biopsies.[38,39] Last, in the case of local tumor recurrence, whereby it can be difficult to distinguish between posttreatment changes and local recurrence, PET/CT-guided biopsies may be of value.

Accurate staging of MPNST is important for treatment planning and prognostic stratification. It has been demonstrated that most MPNST are high-grade sarcomas, with a high probability of local recurrence and distant metastasis. In total, 40% to 65% of MPNST cases experience local recurrence and 30% to 60% develop metastases.[40–42] Approximately 65% of MPNST metastases are to the lungs, with the liver, brain, bones, and adrenal glands also being common sites of distant spread. Regional lymph node involvement is infrequent, and for this reason, lymph node dissection should not be regularly done.[4]

Overall, PET/CT has a noteworthy effect on staging and restaging sarcomas particularly for lymph nodal metastases, distant metastases, and local relapse. Local recurrence can often be difficult to distinguish from posttreatment changes. In a study of 47 patients with MPNST, Khiewvan and colleagues[43] demonstrated 100% sensitivity for PET/CT to detect locally recurrent disease compared with 86% with conventional CT imaging. Furthermore, the PET/CT scans detected significantly more distant sites of disease, resulting in treatment changes in 31% of patients undergoing initial staging examinations. However, the sensitivity has been shown to be lower for lung metastases; thus, nodules found on diagnostic CT should be suspect in the appropriate clinical setting, even in the absence of increased metabolically activity. In conclusion, PET/CT can more accurately stage and restage

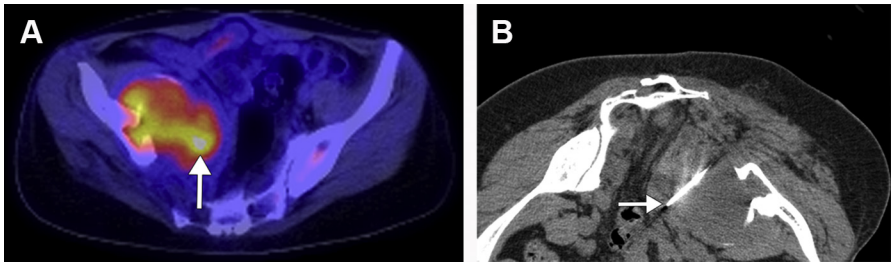

Fig. 4. A 34-year-old female patient with history of NF1 and pelvic mass. 18F-FDG PET/CT (*A*) shows heterogeneous hypermetabolism of the right pelvis mass (*arrow*) with an SUVmax of 12.3 and erosion of the right ilium. CT-guided biopsy (*B*) targeted the most hypermetabolic medial aspect of the mass (*arrow*), which was diagnosed to be an MPNST.

patients with PNT and may result in a paradigm shift in patient management strategy.

THERAPY RESPONSE ASSESSMENT AND PROGNOSIS OF MALIGNANT PERIPHERAL NERVE SHEATH TUMORS WITH FLUDEOXYGLUCOSE-PET/COMPUTED TOMOGRAPHY

The literature addressing the utility of FDG-PET/CT for therapy response assessment and prognosis for MPNST is scarce. At present, most STS cases, particularly those with intermediate and high grades, are treated with neoadjuvant chemotherapy or radiotherapy before surgical resection.[44] Precise noninvasive evaluation of therapy response would be of great value for STS treatment to better guide therapeutic decisions and avoid ineffective chemotherapy or radiation treatment. The RECIST criteria for solid tumors have been shown to be ineffective for sarcoma treatment response evaluation.[45,46] This demerit is due to the fact that most of these tumors encompass structural parts, hindering tumor shrinkage after cytotoxic therapy. Therefore, several reports have revealed that metabolic imaging with FDG-PET/CT is superior to morphologic imaging such as MR imaging or CT in therapy response evaluation in STS.[47–49]

In patients with STS, it is imperative to identify prognostic parameters to delineate the best management strategy and follow-up examinations. Although factors such as large tumor size and intermediate- or high-grade histology are associated with reduced survival, numerous studies have focused on the relation between tumor FDG uptake and tumor necrosis, with higher levels of tumor necrosis a strong predictor of long-term therapy response.[44,50–52]

Moreover, as noted above, it is frequently problematic to diagnose local recurrence of STS due to changes in the normal anatomy by prior manipulations such as surgery or radiotherapy. Based on the small number of reports regarding this issue, PET imaging has demonstrated a high sensitivity for the revealing of local recurrence in high-grade STS, although diagnosis of recurrences of low-grade tumors cannot be anticipated from FDG-PET.[43,53,54] Despite the potential implication of FDG-PET/CT in the diagnosis of STS recurrence, the application of FDG-PET into the follow-up strategy of STS patients is not yet well characterized.

NEW PARAMETERS AND RADIOTRACERS

Novel parameters such as metabolic tumor volume and total lesion glycolysis have been used in prior studies with promising results.[19,31,55,56] In addition, Derlin and colleagues[24] have evaluated the utility of the Homogeneity Index SUV, incorporating the metabolic homogeneity of a lesion, which has resulted in increasing specificity between benign and malignant lesions. However, SUVmax remains the most supported parameter in the literature, and further investigations into these novel parameters are required to elucidate their clinical significance. In view of multitracer PET imaging, it has been demonstrated that intertumoral and intratumoral heterogeneity of blood flow and angiogenesis, hypoxia, necrosis, cellular proliferation, gene mutation, and expression of specific receptors can be evaluated with FDG and non-FDG-PET radiotracers, potentially assisting in medical decision making in the era of personalized medicine.[52,57,58]

In a study of 22 patients with schwannomas, Ahmed and colleagues[59] compared 18F FDG-PET to 18F-fluoro-α-methyl tyrosine (18FMT), an amino acid tracer that monitors protein metabolism, and concluded that 18FMT-PET is more accurate for distinction between benign schwannoma and malignancy than 18FDG-PET. In addition, prostate-specific membrane antigen (PSMA), a transmembrane glycoprotein primarily expressed by prostate cells and other tissues (eg, small intestine, renal tubules, or salivary glands),[60] was noted in the endothelium of tumor-associated neovasculature in some solid cancers such as MPNST, possibly due to the effect of tumor-associated angiogenic factors.[61–64] Somatostatin receptor agonists such as DOTA-TATE have also been proven to have valuable effects on the management of neuroendocrine cancers, indicating value for these radiotracers in the clinical management of somatostatin-avid cancers,[65] such as PNTs.[66–69] Furthermore, PSMA and DOTA-TATE also can be bound with radionuclides such as gallium-68 and lutetium-177 to develop radiopharmaceuticals for both PET imaging and radionuclide therapy.

SUMMARY

In conclusion, FDG-PET, especially in conjunction with CT, is a useful imaging modality for patients with PNT with many advantages over conventional imaging. This modality can aid in the diagnosis, staging, and restaging of PNT as well as in image-guided biopsy. Furthermore, FDG-PET may serve a role in the grading of PNT and assist in determining prognosis and treatment response, although additional data are needed. The use of FDG-PET/CT for PNT can significantly affect

clinical management and enables the implementation of precision medicine, an emerging theme for future clinical practice. In addition, a growing body of evidence supports the use of hybrid PET-MR imaging and alternative radiotracers in PNT.

This overview provides insights into the usefulness of PET in peripheral nerve oncology and how it can assist in providing optimal patient care. However, additional studies evaluating FDG-PET and the development of more specific radiotracers are still needed to improve the performance of PET in the assessment of PNT.

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